REMARKS

Reconsideration of this application is respectfully requested. Claims 1 and 4 have been amended to recite that the method includes feeding a sow a sufficient amount of L-carnitine (or a salt thereof) and chromium tripicolinate to enhance its farrowing rate. Support for this amendment is found at, for example, page 6, lines 7-9, and page 8, lines 3-7, of the application. Claims 16 and 17 have been added. Support for these claims is found at, for example, original claims 1-3. Claims 1, 2, 4, 5, 16, and 17 are pending and at issue.

Applicants gratefully acknowledge the courtesies shown by the Examiner during telephone interviews on February 2nd and 3rd in which the present claim amendments were discussed.

Claims 1-6 have been rejected under 35 U.S.C. §103(a) as obvious over:

(1) Musser et al., "Effects of L-Carnitine on Performance of Gestating and Lactating Sows", *Swine Day* (1997),

(2) Trottier et al., "Effect of Supplemental Chromium Tripicolinate on Sow Productivity and Blood Metabolites" (1998),

(3) J. Arthington, Millennium Technologies, "The Original L-Carnitine/Chromium Picolinate Supplement. How and Why it Works?", (April 27, 2000), and

(4) Samland et al. ("Samland III"), "Effect of L-Carnitine and Chromium Nicotinate on the Ovulation and Fertilization Rate of Gilts", *Proceedings of American Association of Swine Practitioners* (March 1999).

Applicants respectfully traverse this rejection, and request reconsideration.

As acknowledged by the Examiner in the January 18, 2005 Advisory Action, while Arthington discloses the combination of L-carnitine and chromium picolinate, it does not teach

enhancing reproductive performance in sows with it. The Examiner, however, contends that it would have been obvious to employ this combination for enhancing reproductive performance since (1) Arthington teaches that chromium is necessary for optimal insulin function and glucose uptake in cells and L-carnitine aids fatty acid metabolism and (2) Samland III teaches that increased insulin secretion has been shown to increase maturation of ovarian follicles and ovulation rate. The Examiner further concludes that "the strength of correlation between [the] references gives rise to [a] reasonable expectation of success from combining them." *See* January 18, 2005 Advisory Action.

The prior art taken as a whole, however, does not provide a reasonable expectation of success for enhancing reproductive performance, such as the farrowing rate of a sow, with the combination of L-carnitine and chromium tripicolinate. For clarification, the term "farrowing rate" is defined as the number of females farrowed divided by the number of females bred excluding the number of sows removed for nonproductive reasons after mating. *See* Koketsu et al., *J. Anim. Sci.* 75:2580-2587 (1997) (a copy of which is submitted herewith). The farrowing rate is influenced by a number of factors, including fertilization rate, embryonic mortality during the first weeks of pregnancy, and ovulation rate.

Only one study involving treatment with the combination of L-carnitine and chromium for enhancing reproductive performance has been reported. *See* Samland *et al.* ("Samland II"), "Ovulation and Fertilization Rate of Gilts Provided Additional L-Carnitine and Chromium Nicotinate", *Swine Day 1998* (November 1998); and Samland III. In that study (Samland II and III), treatment with 200 ppm L-carnitine alone resulted in statistically significant improved ovulation rates ($p < 0.6$) in gilts, while treatment with the combination of 200 ppm L-carnitine and

200 ppb chromium nicotinate ($P < 0.28$) did not. *See* Samland III at 33 ("An increase ($P=0.6$; Table 1) in ovulation rate was observed for gilts on ... added L-carnitine treatments"), 35 (Table 1). The L-carnitine treatment, however, resulted in fewer fertilized eggs. *See* Samland III at 33-34 ("Fewer ($P=0.04$) fertilized eggs were observed when gilts were fed added L-carnitine"). The fact that no differences were observed for the percentage of embryos shows that the positive effect of L-carnitine on the ovulation rate is completely diminished by its negative effect on the fertilization rate. *Id.* at 33. The reported results show no beneficial reproductive effect with the combination. *See* Samland III at the paragraph spanning pages 33 and 34, 35 (Table 1).

Also, in Samland III, it is stated that there were tendencies for fewer eggs to be recovered from gilts fed chromium nicotinate, which seemed to be due to numerically fewer ovulations for gilts receiving this treatment (*Id.* at 33, right column, last paragraph). This suggests that treatment with chromium results in a decreased farrowing rate. Furthermore, none of the cited references show that chromium enhances farrowing rate.

Therefore, Samland II and III teach away from using a combination of L-carnitine and chromium to enhance reproductive performance.

In the introduction of Samland III, the authors note that "[i]ncreased insulin secretion has been shown to increase maturation of ovarian follicles and ovulation rate (Cox et al., 1987)" (Samland III, page 33, left column). The authors further note that both L-carnitine and chromium picolinate have been shown to increase insulin function. *Id.* Based on these prior results, the authors decided to "[evaluate] the effects of L-carnitine and chromium nicotinate" on ovulation and fertilization rates in gilts. *Id.* The Examiner similarly relies on these prior findings discussed in

Samland III to show that it would have been obvious to try the combination of L-carnitine and chromium to enhance reproductive performance:

> Samland et al. ... teaches that increased insulin secretion has been shown to increase maturation of ovarian follicles and ovulation rate ... Thus, it would have been obvious to employ [a] synergistic combination of L-carnitine and trivalent chromium to enhance reproductive performance motivated by the teaching of Samland et al. that the synergistic combination of Arthington would increase maturation of ovarian follicles and ovulation rate.

See the January 18, 2005 Advisory Action.

While one of ordinary skill in the art might expect the combination to increase insulin secretion greater than L-carnitine alone and, therefore, result in greater improvement in ovulation rate (which is not admitted here), the opposite was found. L-carnitine alone was found to improve ovulation rate while the combination did not. Samland III at 33, 35. None of the treatments increased plasma insulin concentrations. *Id.* at 33 (right column, "Plasma Analysis"). No reproductive benefits for the combination of L-carnitine and chromium nicotinate were found. *Id.* at 33, 35. Accordingly, one of ordinary skill in the art would not have had a reasonable expectation of success for enhancing reproductive performance in sows with the combination of L-carnitine and chromium tripicolinate based on the experimental results in Samland II or III or the prior art as a whole.

Additionally, Musser shows that there is no direct relationship between increased insulin secretion and farrowing rate in sows. Sows treated with 50 ppm L-carnitine exhibited increased insulin concentrations (Table 6 on page 37). However, L-carnitine fed to sows during gestation was found to *decrease* the sows' farrowing rate from 96.1% (no L-carnitine was fed) to 86.5% (L-carnitine fed only during gestation) or 93.2% (L-carnitine fed during gestation and lactation) (Table

5 on page 36). After statistical analysis, Musser concludes that "No differences were observed in subsequent days to estrus or farrowing rate ..." (page 33, top right column). This is directly contrary to the Examiner's contention that increased insulin secretion results in increased farrowing rate. This also teaches away from feeding a sufficient amount of L-carnitine with chromium tripicolinate during gestation and optionally lactation, breeding, and/or pre-breeding to enhance the farrowing rate of the sow as recited in the pending claims.

Neither Musser nor Trottier disclose or suggest (1) feeding a combination of L-carnitine and chromium tripicolinate, or (2) that such a combination can be fed to a sow in sufficient amounts to enhance its farrowing rate as required by the pending claims. Trottier did not study or discuss farrowing rates. See page 5 of the November 19, 2004 Amendment. Accordingly, neither Musser nor Trottier provides a reasonable expectation of success for enhancing farrowing rate with the combination of L-carnitine and chromium tripicolinate.

Arthington describes that L-carnitine influences fat and protein metabolism in pigs by increasing the breakdown of fat, increasing protein synthesis rates and decreasing 10th rib backfat. Similar effects are described for chromium picolinate (reduction in 10th rib back fat, increase in carcass protein). Arthington further discloses that both compounds work synergistically to reduce the amount of fat depostion during the protein phase of growth despite their different modes of action.

However, from Arthington, it is clear that both substances work synergistically only in this very specific phase of growth and development. Arthington does not disclose or suggest that both substances will work synergistically in other developmental phases such as reproduction (e.g., ovulation, fertilization, and/or gestation). Two substances which act synergistically during one

developmental phase do not necessarily act synergistically in a completely different development phase for a completely different purpose.

None of the cited references provide a reasonable expectation of success for enhancing reproductive performance of sows by feeding them a sufficient amount of L-carnitine (or a salt thereof) and chromium tripicolinate to enhance their farrowing rate. It was surprisingly discovered that the combination of L-carnitine and chromium picolinate significantly increases the farrowing rate of sows after two parities as shown by Example 1 of the present application.

For the foregoing reasons, the cited references alone or in combination fail to render obvious the presently claimed invention. Applicants respectfully request withdrawal of this rejection.

In view of the foregoing remarks, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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